

L Number	Hits	Search Text	DB	Time stamp
1	2	("5691153").PN.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/01/16 12:15
2	11	carulli NEAR john	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/01/16 12:16
3	16	Recker NEAR Robert	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/01/16 12:17
4	19	High ADJ bone ADJ mass	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/01/16 12:17
5	3	zmax1 and bone	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/01/16 12:18
6	0	(ldl NEAR receptor) AND (high ADJ bone ADJ mass)	DERWENT	2004/01/16 12:19
7	13	(US-6545137-\$ or US-5691153-\$ or US-6555654-\$ or US-6620427-\$).did. or (US-20020055139-\$ or US-20030026860-\$ or US-20030219793-\$).did. or (WO-9846743-\$ or DE-1241819-\$ or WO-200292015-\$ or WO-200192891-\$ or WO-200177327-\$ or US-5691153-\$).did.	USPAT; US-PGPUB; DERWENT	2004/01/16 12:19

FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, MEDICONF' ENTERED
AT 12:24:14 ON 16 JAN 2004

L1 146 S HIGH BONE MASS
L2 78 DUP REM L1 (68 DUPLICATES REMOVED)
L3 8 S L2 AND LDL?
L4 8 SORT L3 PY
E CARULLI J?/AU
L5 19 S E7
L6 30 S E2
L7 0 S L5 AND L6
L8 49 S L5 OR L6
L9 24 DUP REM L8 (25 DUPLICATES REMOVED)
L10 3 S L9 AND L1

=> d an ti so au ab pi l10 1-3

L10 ANSWER 1 OF 3 MEDLINE on STN
AN 2001694099 MEDLINE
TI A mutation in the LDL receptor-related protein 5 gene results in the
autosomal dominant **high-bone-mass** trait.
SO AMERICAN JOURNAL OF HUMAN GENETICS, (2002 Jan) 70 (1) 11-9.
Journal code: 0370475. ISSN: 0002-9297.
AU Little Randall D; Carulli John P; Del Mastro Richard G; Dupuis
Josee; Osborne Mark; Folz Colleen; Manning Susan P; Swain Pamela M; Zhao
Shan-Chuan; Eustace Brenda; Lappe Michelle M; Spitzer Lia; Zweier Susan;
Braunschweiger Karen; Benchekroun Youssef; Hu Xintong; Adair Ronald; Chee
Linda; FitzGerald Michael G; Tulig Craig; Caruso Anthony; Tzellas Nia;
Bawa Alicia; Franklin Barbara; McGuire Shannon; Nogues Xavier; Gong
Gordon; Allen Kristina M; Anisowicz Anthony; Morales Arturo J; Lomedico
Peter T; Recker Susan M; Van Eerdewegh Paul; Recker Robert R; Johnson Mark
L
AB Osteoporosis is a complex disease that affects >10 million people in the
United States and results in 1.5 million fractures annually. In addition,
the high prevalence of osteopenia (low bone mass) in the general
population places a large number of people at risk for developing the
disease. In an effort to identify genetic factors influencing bone
density, we characterized a family that includes individuals who possess
exceptionally dense bones but are otherwise phenotypically normal. This
high-bone-mass trait (HBM) was originally
localized by linkage analysis to chromosome 11q12-13. We refined the
interval by extending the pedigree and genotyping additional markers. A
systematic search for mutations that segregated with the HBM phenotype
uncovered an amino acid change, in a predicted beta-propeller module of
the low-density lipoprotein receptor-related protein 5 (LRP5), that
results in the HBM phenotype. During analysis of >1,000 individuals, this
mutation was observed only in affected individuals from the HBM kindred.
By use of in situ hybridization to rat tibia, expression of LRP5 was
detected in areas of bone involved in remodeling. Our findings suggest
that the HBM mutation confers a unique osteogenic activity in bone
remodeling, and this understanding may facilitate the development of novel
therapies for the treatment of osteoporosis.

L10 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:886643 CAPLUS
DN 136:32816
TI Regulating lipid levels via the human Zmax1 or **high-bone**
-mass HBM gene
SO PCT Int. Appl., 409 pp.
CODEN: PIXXD2
IN Carulli, John P.; Little, Randall D.; Recker, Robert R.;
Johnson, Mark L.
AB The present invention relates to the **high bone**
mass (HBM) gene, the corresponding wild-type gene (Zmax1), and
mutants thereof. The Zmax1/HBM gene was located on chromosome 11q13.3 by
genetic linkage and mutation anal. Cloning methods using bacterial
artificial chromosomes enabled focus on the chromosome region of 11q13.3
and sequencing of the autosomal dominant gene. A guanine-to-thymine
polymorphism at position 582 (glycine-to-valine at position 171 in the
protein) in Zmax1 gene produces the HBM gene and the HBM phenotype as well
as altered lipid levels. Hybridization for Zmax1 is primarily detected in

areas of bone involved in remodeling, including the endosteum and trabecular bone within the metaphysis; pos. signals are also obsd in selected bone lining cells of the periosteum and epiphysis and in chondrocytes within the growth plate. The genes identified in the present invention are implicated in regulation of physiol. lipid levels, and thereby lipid-mediated diseases and conditions. The invention also provides nucleic acids, including coding sequences, oligonucleotide primers and probes, proteins, cloning vectors, expression vectors, transformed hosts, methods of developing pharmaceutical compns., methods of identifying mols. involved in lipid level regulation in a subject. In preferred embodiments, the present invention is directed to methods for treating and preventing atherosclerosis, arteriosclerosis cardiovascular disease, atherosclerotic and arteriosclerotic assocd. conditions.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001092891	A2	20011206	WO 2001-US16946	20010525
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
EP 1285002	A2	20030226	EP 2001-948240	20010525
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
BR 2001011057	A	20030415	BR 2001-11057	20010525

L10 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN

AN 2001:763189 CAPLUS

DN 135:328141

TI Human gene Zmax1 of 11q13.3, HBM (**high bone mass**) allele, encoded polypeptides, and their diagnostic and therapeutic uses

SO PCT Int. Appl., 443 pp.
CODEN: PIXXD2

IN Carulli, John P.; Little, Randall D.; Recker, Robert R.; Johnson, Mark L.

AB The present invention relates to methods and materials used to isolate and detect a **high bone mass** gene and a corresponding wild-type gene, and mutants thereof. The present invention also relates to the **high bone mass** allele, the corresponding wild-type gene, Zmax1, and mutants thereof. The genes identified in the present invention are implicated in bone development and in focal adhesion signaling. The invention also provides nucleic acids, including coding sequences, oligonucleotide primers and probes, proteins, cloning vectors, expression vectors, transformed hosts, methods of developing pharmaceutical compns., methods of identifying mols. involved in bone development, and methods of diagnosing and treating diseases involved in bone development. In preferred embodiments, the present invention is directed to methods for treating, diagnosing and preventing osteoporosis. The invention describes expanded pedigree anal. and genetic linkage anal. of a **high bone mass** (HBM) gene now known as an allele of human gene Zmax1. Older individuals with the HBM allele do not show loss of bone mass compared to normal individuals, do not have osteoporosis, and do not have any known **high bone mass** syndrome. Gene Zmax1 was localized between genetic markers on human chromosome 11q13.3 and subsequently, BAC clones with the gene were sequenced. The HBM allele is inherited as an autosomal dominant gene and is a G.fwdarw.T mutation at nucleotide 582 in exon 3 which results in a G171V substitution in the encoded protein. Addnl. genotyping of 911 individuals established that the HBM allele is rare and never found in unaffected individuals. "Silent" SNPs (single nucleotide polymorphisms) in the gene Zmax1 region were also identified. Gene Zmax1 encodes an LDL-receptor-related protein and the HBM mutation occurs in a conserved region of the presumed extracellular domain. Proteins interacting with the cytoplasmic domain of gene Zmax1 protein in a yeast two-hybrid assay were identified and include many proteins found at

cell-cell and cell-matrix contact sites. These results suggest a potential role for gene Zmax1 in focal adhesion signaling and suggest that regulating gene Zmax1 expression or protein binding may affect bone processes.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001077327	A1	20011018	WO 2000-US16951	20000621
W:				
				AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW:				GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
EP 1268775	A1	20030102	EP 2000-941578	20000621
R:				AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL
US 2003219793	A1	20031127	US 2003-374979	20030228

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
 DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
 CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
 EP 1268775 A1 20030102 EP 2000-941578 20000621
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL
 US 2003219793 A1 20031127 US 2003-374979 20030228

L4 ANSWER 2 OF 8 MEDLINE on STN

AN 2002311732 MEDLINE

TI Localization of the gene causing autosomal dominant osteopetrosis type I to chromosome 11q12-13.

SO JOURNAL OF BONE AND MINERAL RESEARCH, (2002 Jun) 17 (6) 1111-7.
 Journal code: 8610640. ISSN: 0884-0431.

AU Van Hul Els; Gram Jeppe; Bollerslev Jens; Van Wesenbeeck Liesbeth;
 Mathysen Danny; Andersen Poul Erik; Vanhoenacker Filip; Van Hul Wim

AB The osteopetroses are a heterogeneous group of genetic conditions characterized by increased bone density due to impaired bone resorption by osteoclasts. Within the autosomal dominant form of osteopetrosis, the radiological type I (ADOI) is characterized by a generalized osteosclerosis, most pronounced at the cranial vault. The patients are often asymptomatic but some suffer from pain and hearing loss. ADOI is the only type of osteopetrosis not associated with an increased fracture rate. Linkage analysis in two families with ADOI from Danish origin enabled us to assign the disease-causing gene to chromosome 11q12-13. A summated maximum lod score of +6.54 was obtained with marker D11S1889 and key recombinants allowed delineation of a candidate region of 6.6 cM between markers D11S1765 and D11S4113. Previously, genes causing other conditions with abnormal bone density have been identified from this chromosomal region. The TCIRG1 gene was shown to underly autosomal recessive osteopetrosis (ARO), and, recently, mutations in the LRP5 gene were found both in the osteoporosis-pseudoglioma syndrome and the **high bone mass** trait. Because both genes map within the candidate region for ADOI, it can not be excluded that ADOI is caused by mutations in either the TCIRG1 or the LRP5 gene.

L4 ANSWER 3 OF 8 MEDLINE on STN

AN 2002274995 MEDLINE

TI High bone density due to a mutation in LDL-receptor-related protein 5.

SO NEW ENGLAND JOURNAL OF MEDICINE, (2002 May 16) 346 (20) 1513-21.
 Journal code: 0255562. ISSN: 1533-4406.

AU Boyden Lynn M; Mao Junhao; Belsky Joseph; Mitzner Lyle; Farhi Anita;
 Mitnick Mary A; Wu Dianqing; Insogna Karl; Lifton Richard P

AB BACKGROUND: Osteoporosis is a major public health problem of largely unknown cause. Loss-of-function mutations in the gene for low-density lipoprotein receptor-related protein 5 (LRP5), which acts in the Wnt signaling pathway, have been shown to cause osteoporosis-pseudoglioma. METHODS: We performed genetic and biochemical analyses of a kindred with an autosomal dominant syndrome characterized by high bone density, a wide and deep mandible, and torus palatinus. RESULTS: Genetic analysis revealed linkage of the syndrome to chromosome 11q12-13 (odds of linkage, >1 million to 1), an interval that contains LRP5. Affected members of the kindred had a mutation in this gene, with valine substituted for glycine at codon 171 (LRP5V171). This mutation segregated with the trait in the family and was absent in control subjects. The normal glycine lies in a so-called propeller motif that is highly conserved from fruit flies to humans. Markers of bone resorption were normal in the affected subjects, whereas markers of bone formation such as osteocalcin were markedly elevated. Levels of fibronectin, a known target of signaling by Wnt, a developmental protein, were also elevated. In vitro studies showed that the normal inhibition of Wnt signaling by another protein, Dickkopf-1 (Dkk-1), was defective in the presence of LRP5V171 and that this resulted in increased signaling due to unopposed Wnt activity. CONCLUSIONS: The LRP5V171 mutation causes high bone density, with a thickened mandible and torus palatinus, by impairing the action of a normal antagonist of the Wnt pathway and thus increasing Wnt signaling. These findings demonstrate the role of altered LRP5 function in **high bone mass** and point to Dkk as a potential target for the prevention or treatment of osteoporosis.